RESEARCH PAPER

Design, Optimization, and Evaluation of a Lovastatin-Loaded Nanoemulsion-Based Nanoemulgel for Enhanced Solubility and Controlled Topical Drug Delivery

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ABSTRACT

Lovastatin, a BCS class II drug, exhibits poor aqueous solubility and variable therapeutic performance, limiting its clinical effectiveness. The present study aimed to develop and optimize a lovastatin-loaded nanoemulsion and further incorporate it into a nanoemulgel system to enhance solubility and achieve controlled topical drug delivery.

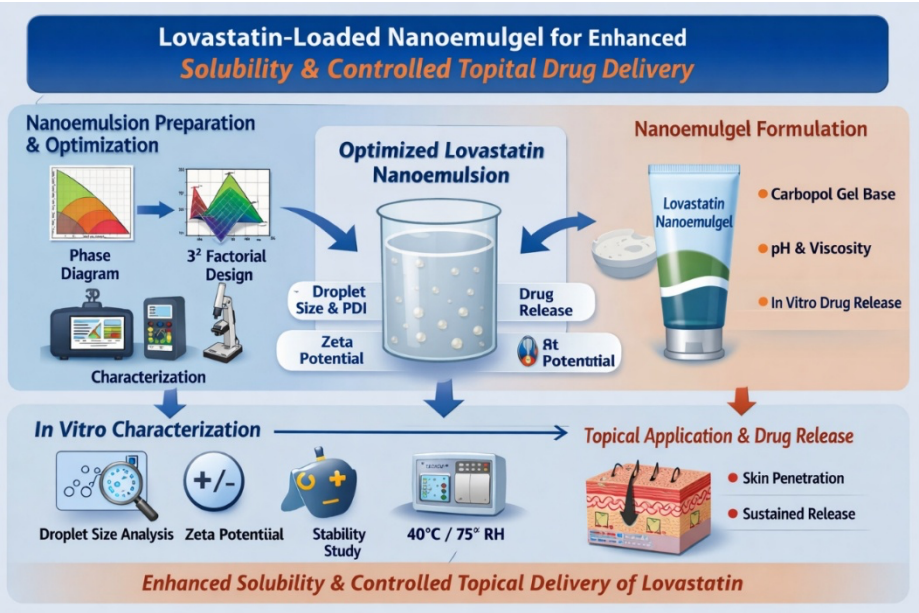
Preformulation studies were conducted to evaluate the physicochemical properties and solubility behavior of the formulation. Suitable oils, surfactants, and co-surfactants were selected based on solubilization capacity and emulsification efficiency. A pseudo-ternary phase diagram was constructed to identify the nanoemulsion region. A 3^2 full factorial design was employed to optimize formulation variables, namely, oil concentration (X_1) and Smix concentration (X_2), with percent transmittance, viscosity, and drug release as responses.

The optimized nanoemulsion exhibited high clarity (99.45% transmittance), appropriate viscosity (~140 cP), nanoscale droplet size with uniform distribution, and enhanced drug release (~86% over 8 h). The optimized system was incorporated into a carbopol-based gel to obtain a nanoemulgel with a suitable pH, good spreadability, and homogeneity. The nanoemulgel demonstrated sustained drug release (~92% over 12 h), indicating its potential for prolonged topical delivery.

Statistical analysis confirmed that oil concentration significantly influenced formulation performance, whereas Smix improved drug release and clarity. Short-term stability studies indicated no significant changes in the physicochemical properties.

Overall, the developed nanoemulsion-based nanoemulgel represents a promising approach for enhancing the solubility and controlled topical delivery of lovastatin, warranting further investigation using ex vivo and in vivo studies.

Graphical abstract:



Highlights

• Developed a lovastatin-loaded nanoemulsion using a systematic Design of Experiments (3^2 factorial design) approach
• Optimized formulation demonstrated high clarity, nanoscale droplet size, and enhanced drug release
• Nanoemulsion was successfully incorporated into a Carbopol-based nanoemulgel for topical delivery
• Nanoemulgel exhibited suitable physicochemical properties with sustained drug release up to 12 h
• Oil and Smix concentrations were identified as critical factors influencing formulation performance
• The developed system offers a promising strategy for improving solubility and controlled topical delivery of poorly water-soluble drugs

Keywords: Lovastatin, Nanoemulsion, Nanoemulgel, Design of Experiments (DoE), Solubility enhancement, Controlled drug release, Topical drug delivery, Lipid-based drug delivery, Carbopol gel, BCS Class II drug
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INTRODUCTION

Lovastatin is a first-generation lipid-lowering agent widely used to manage hypercholesterolemia and prevent cardiovascular diseases by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. However, its clinical performance is significantly limited by poor aqueous solubility and extensive first-pass metabolism, classifying it as a biopharmaceutical classification system (BCS) class II drug. These limitations result in dissolution rate-limited absorption and variable therapeutic outcomes, thereby necessitating the development of advanced drug delivery systems to enhance its solubility and performance [1–3].

Lipid-based nanocarrier systems, such as nanoemulsions, have emerged as promising approaches for improving the solubility and dissolution of poorly water-soluble drugs. Nanoemulsions are isotropic dispersions consisting of oil, water, surfactant, and co-surfactant, with droplet sizes in the nanometer range. These systems enhance drug solubilization, increase surface area, and improve drug permeation across biological membranes [4,5]. Recent studies have demonstrated that nanoemulsions significantly enhance drug release and topical delivery of lipophilic compounds owing to their small droplet size and thermodynamic stability [6,7].

Nanoemulgels represent an advanced drug delivery platform formed by incorporating nanoemulsions into gel matrices, combining the advantages of both systems. This approach improves formulation stability, enhances patient compliance, and provides controlled drug release. Recent reviews and research studies have highlighted nanoemulgels as effective carriers for topical drug delivery, offering improved permeation and sustained therapeutic effects [8–10]. Furthermore, nanoemulgel systems have demonstrated superior performance compared to conventional gels in delivering poorly soluble drugs through the skin barrier [11].

The application of systematic formulation strategies, such as quality by design (QbD) and design of experiments (DoE), has become increasingly important in the development of nanocarrier systems. These approaches enable the identification of critical formulation variables and their interactions, leading to robust and optimized formulations. Factorial design methods have been widely used to optimize nanoemulsion formulations and improve drug delivery performance [12,13]. Additionally, stability considerations based on regulatory guidelines are essential to ensure formulation robustness and shelf life [14].

Recent advancements in nanotechnology-based drug delivery have demonstrated the effectiveness of nanoemulsion and nanoemulgel systems in enhancing drug solubility, permeability, and sustained release. These systems have been successfully applied to a variety of lipophilic drugs, highlighting their potential in overcoming formulation challenges associated with poor aqueous solubility [15–18]. Moreover, the integration of lipid-based carriers with polymeric gel systems has further improved topical drug delivery efficiency and therapeutic outcomes [19,20].

Despite these advancements, there remains a need for systematic optimization of lovastatin nanoemulsion formulations and their transformation into nanoemulgel systems using statistically driven approaches. Therefore, the present study aimed to develop and optimize a lovastatin-loaded nanoemulsion using a 3^2 factorial design and further incorporate it into a carbopol-based nanoemulgel for controlled topical delivery. This study evaluated the influence of formulation variables on critical quality attributes, such as transmittance, viscosity, and drug release.

Thus, this study provides a rational and systematic approach for developing a nanoemulsion-based nanoemulgel system, offering a promising strategy for improving solubility and achieving controlled topical delivery of lovastatin.

MATERIALS AND METHODS

The equipment used for the lovastatin nanoemulsion formulation included an electric weight balance (US-300, Cyber lab, USA) for accurate measurement of materials, a magnetic stirrer (Remi Equipments Pvt. Ltd.) to ensure proper mixing of components, a UV-visible spectrometer (UV-1800, Shimadzu Corporation) for absorbance and drug content analysis, a pH meter (PM100, Welltronix) to measure the pH of the formulations, and a viscometer (DV-E Viscometer) for determining the viscosity of the nanoemulsion and gel formulations.

Methodology

Preformulation Study of Lovastatin

A pre-formulation study was conducted to evaluate the physicochemical properties of a drug substance to develop a stable and effective dosage form.

Organoleptic Characteristics

Organoleptic evaluation of lovastatin was performed to assess its physical characteristics, including appearance, color, and odor. This examination helps to confirm the identity of the drug and detect any physical impurities.

Melting Point Determination

The melting point of lovastatin was determined using the capillary method. A small quantity of the drug was placed in a clean, dry capillary tube and subjected to controlled heating. The temperature at which the drug began to melt was recorded as the melting point. This parameter is useful for assessing the purity and thermal stability of drugs.

Determination of Wavelength Maxima (λmax)

A stock solution was prepared by dissolving 100 mg of lovastatin in 100 mL of methanol in a volumetric flask. From this solution, 1 mL was withdrawn and diluted to 100 mL to prepare the working standard. Further dilutions were performed to obtain concentrations in the range of 2–10 µg/mL. The λmax of lovastatin was determined by scanning the prepared solutions in the wavelength range of 200–400 nm using a double-beam UV–visible spectrophotometer.

Preparation of Calibration Curve for Lovastatin

A stock solution of lovastatin was prepared by dissolving 100 mg of the drug in a small amount of methanol, followed by sonication for a few minutes to ensure complete solubilization. The solution was then diluted to 100 mL using a phosphate buffer (pH 7.4). Serial dilutions were prepared from the stock solution to obtain concentrations in the range of 2–10 µg/mL.

The absorbance of each diluted solution was measured at 238 nm using a UV–visible spectrophotometer. A calibration curve was constructed by plotting the concentration (µg/mL) on the X-axis and absorbance on the Y-axis, and the correlation coefficient (R^2) was calculated to determine linearity.

Identification of Lovastatin by FT-IR Spectroscopy

For FT-IR analysis, a potassium bromide (KBr) pellet was prepared by mixing 1 mg of lovastatin with dry KBr and compressing the mixture using a hydraulic pellet press. The prepared discs were scanned over a wavelength range of 4000–400 cm − 1 using an FT-IR spectrophotometer. The resulting spectrum was compared with the reference spectrum of pure lovastatin to confirm drug identity based on the characteristic functional group peaks.

Solubility Study of Lovastatin

The solubility of lovastatin was evaluated in different solvents to support formulation development. The drug exhibited very low solubility in water, moderate solubility in ethanol and acetone, and high solubility in chloroform and dimethyl sulfoxide (DMSO), indicating its lipophilic nature. These results justify the selection of a lipid-based nanoemulsion system to enhance the solubility and release of lovastatin.

Formulation and Development of Lovastatin Nanoemulsion

Solubility studies:

Lovastatin solubility was evaluated in various oils, surfactants, and co-surfactants to identify suitable excipients for nanoemulsion formulation. Excipients showing the highest solubilizing capacity for lovastatin were considered appropriate for further formulation studies, as higher solubility ensures better drug loading and stability.

Emulsification efficiency studies

Selected surfactants and cosurfactants were further evaluated for their emulsification efficiency based on the number of inversions required to form a stable emulsion and percent transmittance. Excipients that produced clear emulsions with high transmittance and rapid emulsification were preferred.

Selection of Surfactant and Co-surfactant

Based on solubility and emulsification efficiency studies, surfactants and cosurfactants exhibiting high drug solubilization, good emulsification capacity, and high percent transmittance were selected for nanoemulsion preparation. The selected surfactant–cosurfactant combination ensured efficient nanoemulsion formation, improved clarity, and enhanced drug release; therefore, it was used for further formulation and optimization studies.

Pseudo-Ternary Phase Diagram Study

A pseudo-ternary phase diagram was constructed to determine the nanoemulsion region and optimize the

composition of the oil, surfactant, and co-surfactant. In the diagram, each apex of the triangular phase plot represents a component. Oil, Surfactant, and co-surfactant mixture (Smix), and water.

Ternary mixtures with varying oil and Smix compositions were prepared while maintaining a total concentration of 100%. The required quantities of the components were accurately weighed and sonicated for 3 min. Lovastatin (20 mg) was added, and the mixture was gently heated to 45–50°C and vortexed to obtain a homogeneous system. Distilled water was then added dropwise until a clear, transparent formulation was obtained.

The surfactant-to-cosurfactant ratios (Smix) were 1:1, 1:2, 2:1, 3:1, and 1:3. The oil: Smix ratios evaluated included 0.5:9.5, 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1. The amount of water (up to 5 mL) required to form a transparent nanoemulsion was recorded and plotted against the other components in the pseudo-ternary phase diagram to identify the nanoemulsion region.

Preliminary Nanoemulsion Batch Evaluation

The preliminary nanoemulsion batches were prepared using different ratios of oil, Smix, and water selected from the pseudo-ternary phase diagram. These batches were evaluated for percent transmittance, viscosity, and in vitro drug release to assess clarity, flow behavior, and release performance. All preliminary batches formed clear and stable nanoemulsions with high transmittance values. Variations in composition influenced viscosity and drug release, providing useful insights into the effect of formulation variables. The results of this evaluation guided the selection of suitable composition ranges for further optimization using the Design of Experiments (DoE) approach.

Characterization of Nanoemulsion

The developed nanoemulsions were evaluated in terms of the percentage yield, drug content, entrapment efficiency, particle size, and in vitro drug release. The results confirmed nanoscale droplet formation, uniform drug distribution, and enhanced drug release, supporting the suitability of the nanoemulsion for further optimization and development.

Percentage Yield

The percentage yield of the prepared nanoemulsions was determined using the following equation:

$$\%\text{Yield} = \left(\frac{\text{Practical weight of nanoemulsion obtained}}{\text{Theoretical weight of drug + excipients}}\right) \times 100$$

This parameter reflects the efficiency of the formulation process and indicates the extent of material loss during preparation.

Drug Content Determination

A total of 25 mg of the nanoemulsion formulation was accurately weighed and transferred to a 25 mL volumetric flask containing methanol. The mixture was thoroughly shaken to ensure complete sample dissolution. The solution was then filtered through Whatman filter paper to remove any undissolved residues or impurities.

From the filtered solution, 1 mL was withdrawn, transferred to a 10 mL volumetric flask, and diluted with methanol to obtain the sample solution. The absorbance of the resulting solution was measured at 202 nm using a UV–visible spectrophotometer, with methanol as the blank.

The concentration of lovastatin in the nanoemulsion was calculated using a linear regression equation obtained from the calibration curve, and the drug content was expressed as the actual amount of drug present in the formulation.

Entrapment Efficiency

The entrapment efficiency of the nanoemulsions was evaluated using the following formula:

$$\text{Entrapment Efficiency (\%)} = \left(\frac{\text{Actual drug content}}{\text{Theoretical drug content}}\right) \times 100$$

This parameter indicates the percentage of the drug successfully encapsulated within the nanoemulsion system relative to the total amount of drug used during the formulation.

Mean Particle Size Analysis

The mean particle size of the nanoemulsion was determined using an optical microscope and Malvern particle size analyzer. These instruments provide information on the size distribution and homogeneity of the formulation, which play a crucial role in controlling drug release, stability, and bioavailability.

In Vitro Drug Release Study of Nanoemulsion

The in vitro drug release profile was evaluated using a USP Type II (paddle) dissolution apparatus. The dissolution medium comprised 900 mL of phosphate buffer (pH 7.4) maintained at 37.0 ± 0.5°C with the paddle speed set to 150 rpm. A known quantity of the nanoemulsion formulation was placed in a dissolution vessel.

At predetermined intervals (hourly for 8 h), 5 mL of the sample was withdrawn and immediately replaced with an equal volume of fresh dissolution medium to maintain sink conditions. The collected samples were analyzed for drug release by measuring the absorbance at 202 nm using a UV–visible spectrophotometer.

Optimization of Nanoemulsion Using Design of Experiments (DoE)

Experimental Design

Optimization of the lovastatin nanoemulsion was carried out using a 3^2 full factorial design. Oil concentration (X_1) and Smix concentration (X_2) were selected as the independent variables and studied at three levels. Percent transmittance (Y_1), viscosity (Y_2), and percent drug release (Y_3) were selected as the dependent responses to evaluate formulation performance.

Preparation of Factorial Batches

Nine nanoemulsion batches were prepared according to the experimental design by varying oil and Smix concentrations, as per the design matrix. All batches were prepared using the same method and evaluated for the selected responses.

Statistical Analysis

The experimental data were analyzed using regression analysis and fitted to quadratic polynomial models. Analysis of variance (ANOVA) was applied to assess the significance of the models and formulation variables, with $p < 0.05$ considered statistically significant. Response surface and contour plots were generated to visualize the effects of the independent variables. A checkpoint (validation) analysis was performed by comparing the predicted and experimental responses to confirm the reliability of the optimization model.

Preparation of Lovastatin Nanoemulgel

Dose Calculation for Gel Formulation

The dose of lovastatin required for the nanoemulgel was calculated based on a target concentration of 1% w/w. Accordingly, 200 mg of lovastatin was required to prepare 20 g of nanoemulgel.

Preparation of Carbopol Gel Base

Carbopol 980 was weighed and dispersed in distilled water with continuous stirring, and allowed to hydrate completely. Propylene glycol and preservatives (methyl and propyl parabens) were added with gentle stirring. The pH of the dispersion was adjusted using triethanolamine to obtain a clear and homogeneous gel base of a suitable consistency.

Incorporation of Optimized Nanoemulsion into Gel

The optimized lovastatin nanoemulsion was gradually incorporated into the prepared Carbopol gel base under slow and uniform stirring to obtain a homogeneous nanoemulgel. Care was taken to avoid air entrapment during mixing. The final nanoemulgel was evaluated for its physicochemical properties and in vitro drug release.

Characterization of Lovastatin Nanoemulgel

Physical Evaluation

The physical characteristics of the prepared nanoemulgel, including color, texture, clarity, occlusiveness, and washability, were evaluated. These organoleptic properties provide preliminary information regarding patient acceptability and formulation consistency.

pH Determination

The pH of the nanoemulgel was determined using a calibrated digital pH meter. Measurements were performed at room temperature, and the average pH value was recorded. The pH was found to be within the acceptable range for topical formulations, indicating good skin compatibility.

Viscosity Study

The viscosity of the formulation was measured using a Brookfield viscometer. The gel was placed in a 50 mL beaker, and the selected spindle was immersed in the sample. The measurements were taken at a predetermined rotational speed (RPM). This procedure was repeated thrice, and the average viscosity was reported.

Spreadability Study

Spreadability was assessed by placing 1 g of the gel between two glass slides and allowing it to spread under its own weight for approximately 5 min. The diameter of the resulting spread was measured in centimeters and used as an indicator of the ease of gel application.

Homogeneity and Grittiness

A small quantity of gel was rubbed between the thumb and index fingers to examine its consistency, smoothness, and uniformity. Additionally, the formulation was applied to the dorsal surface of the hand to evaluate grittiness. A homogeneous gel without coarse particles indicates uniform dispersion and an acceptable texture.

Drug Content

One gram of the nanoemulgel formulation was transferred to a volumetric flask containing 20 mL of alcohol and stirred for 30 min to extract the drug. The solution was filtered, diluted to 10 mL with alcohol, and 1 mL of this solution was diluted to 10 mL. The absorbance of the final diluted solution was recorded at 202 nm using UV-visible spectrophotometry. The drug content was calculated based on a standard calibration curve.

Drug Release Kinetics

To determine the release mechanism of lovastatin from the nanoemulsion gel, the in vitro release data were fitted to various kinetic models.

Model	Equation	Plot
Zero order	$Q_t = Q_0 - K_0 t$	Q_t vs. t

Model	Equation	Plot
First order	$\ln Q_t = \ln Q_0 - Kt$	$(Q_0 - Q_t)$vs. t
Higuchi	$Q_t = K_h t^{1/2}$	$Q_t$vs. $t^{1/2}$

Where:

Q_t= percent drug released at time t

Q_0= initial drug content in the nanoemulgel

K_0, K, K_h= release rate constants for Zero-order, First-order and Higuchi models respectively

The model with the highest correlation coefficient (R^2) was considered the best-fit kinetic model for drug release.

Accelerated Stability Study

Accelerated stability testing was conducted to assess the impact of environmental factors on the formulation. The optimized nanoemulgel was stored at room temperature for one month, with samples collected on days 0, 15, and 30. These samples were evaluated for changes in physical appearance, pH, viscosity, and drug content. Any variations in these parameters were used to determine the physical and chemical stability of the formulation.

RESULT

Preformulation Studies

Organoleptic Properties and Melting Point

Lovastatin was observed as a white odorless crystalline powder, indicating acceptable physical characteristics. The melting point was found to be in the range of 172–174°C, which is consistent with reported values, confirming the purity of the drug.

UV Spectroscopic Analysis

The maximum wavelength (λmax) of lovastatin was 238 nm in methanol (Figure 1). This wavelength was used for all further quantitative analyses.

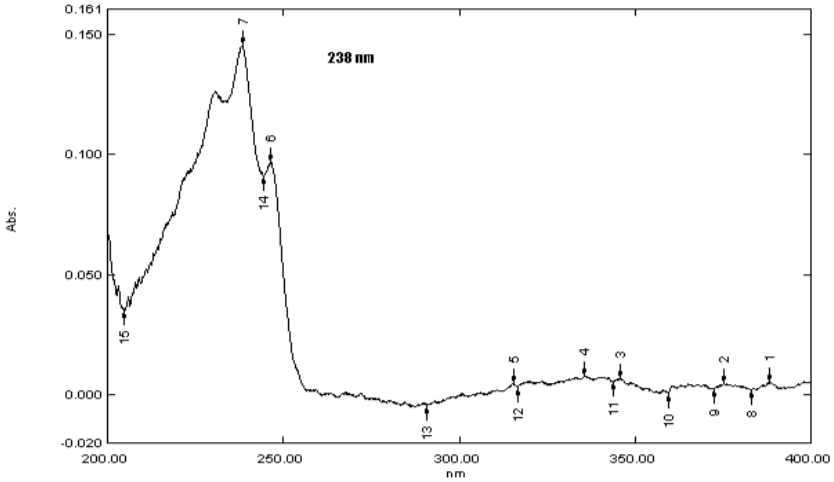


Figure:1 Wavelength max (λmax) of Lovastatin

Calibration Curve The calibration curve of lovastatin showed good linearity in the concentration range of 10–50 µg/mL (Figure 2), with a correlation coefficient (R^2) of 0.9935, indicating reliability of the analytical method.

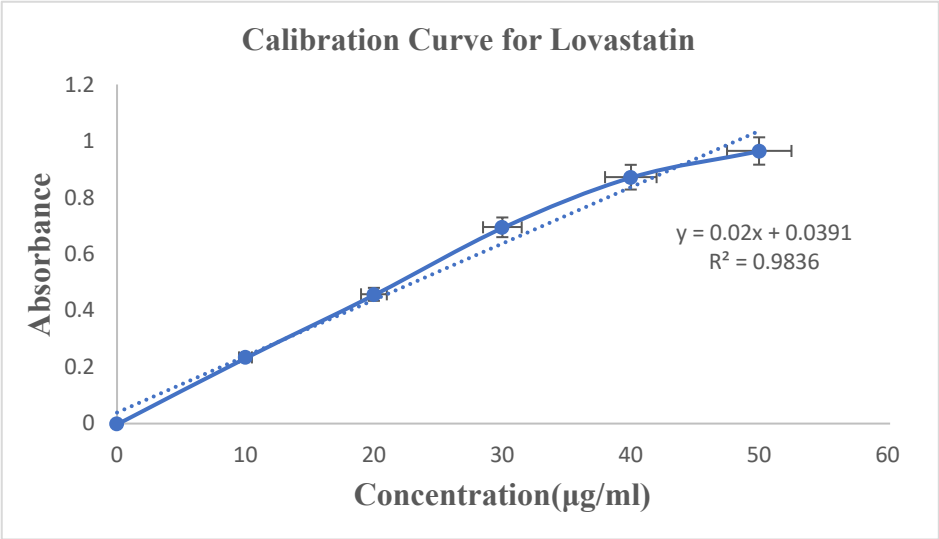


Figure 2 Calibration Curve for Lovastatin

Identification of Drug- Lovastatin by FT-IR Spectroscopy

Pure lovastatin was identified using FT-IR spectroscopy by analyzing its characteristic functional groups based on their infrared absorption peaks. The observed wavenumbers corresponding to the key functional groups, as illustrated in Figure 3, included C=O stretching at 3015 cm^{-1} (standard range: 3100–3000 cm^{-1}), –OH stretching at 2930 cm^{-1} (standard range: 3300–2500 cm^{-1}), a second C=O stretching peak at 1220 cm^{-1} (standard range: 1225–1160 cm^{-1}), and C=C stretching at 1726 cm^{-1} (standard range: 1780–1720 cm^{-1}). These absorption peaks confirmed the presence of the expected functional groups in lovastatin, thereby validating its identity and purity by comparison with standard reference values.

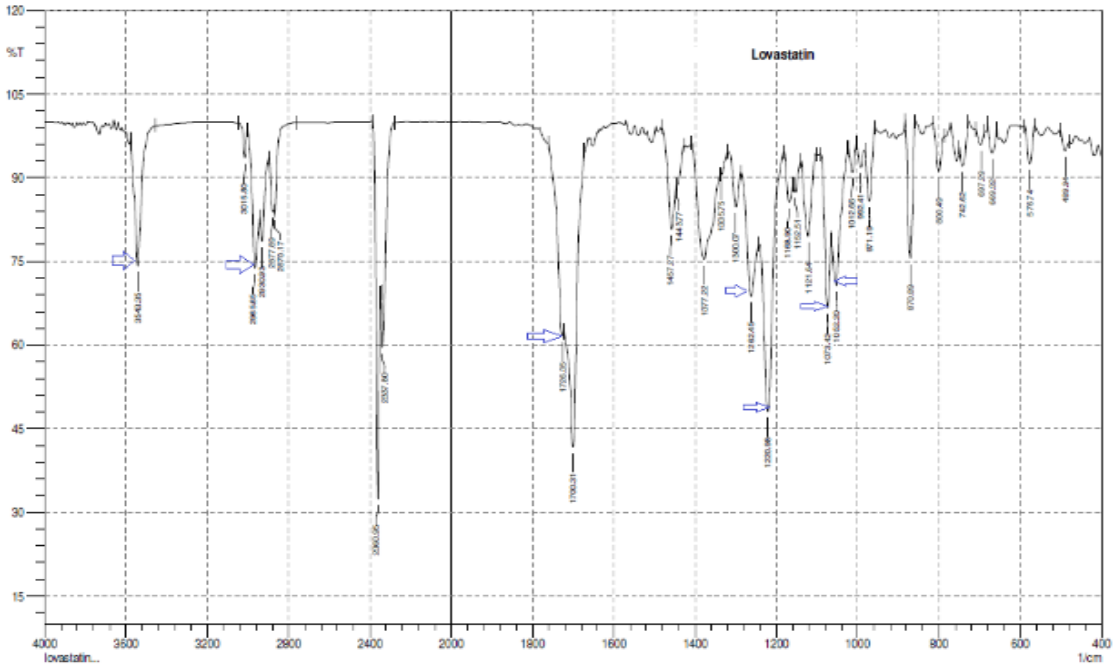


Figure 3 Identification of Pure Drug Lovastatin by IR Spectrum

Solubility study of Lovastatin

Figure 4 presents the solubility profile of lovastatin, which shows that it is slightly soluble in water, with a solubility of 0.0142 mg/mL. It also exhibits limited solubility in ethanol (0.12 mg/mL) and acetone (0.48 mg/mL), while demonstrating high solubility in chloroform at 27.574 mg/mL. Additionally, lovastatin is soluble in dimethyl sulfoxide (DMSO) at 14.54 mg/mL. These findings

highlight the poor aqueous solubility of lovastatin, but its greater solubility in specific organic solvents, an important factor to consider in formulation development aimed at enhancing its bioavailability.

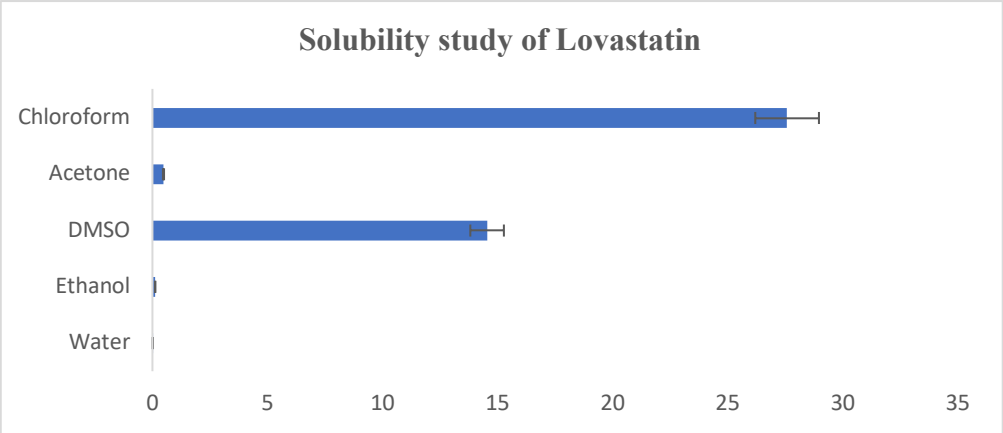


Figure 4 Solubility study of Lovastatin

Screening of Excipients

Screening of Oils, Surfactants, and Co-surfactants

Solubility Screening

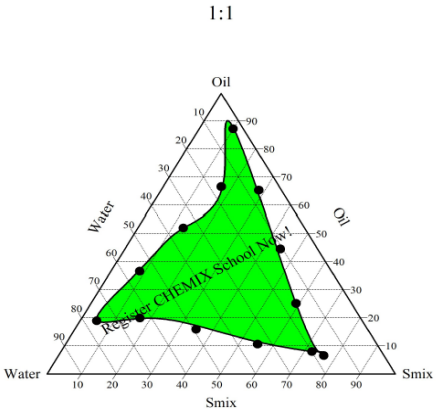
Lovastatin solubility was evaluated using different oils, surfactants, and cosurfactants. Oleic acid exhibited the highest solubility among the oils, whereas Tween 80 and propylene glycol showed better solubilization among the surfactants and cosurfactants, respectively.

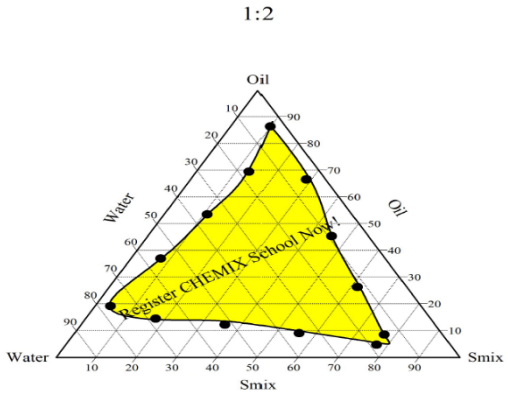
Emulsification Efficiency

Emulsification efficiency was evaluated based on inversion cycles and percent transmittance. Tween 80 exhibited high transmittance, whereas propylene glycol showed excellent emulsification behavior.

Construction of pseudoternary phase diagram

Figure 5 illustrates the pseudoternary phase diagram constructed using oil, Smix (surfactant–co-surfactant mixture), and water. The nanoemulsion region identified in the diagram indicates the compositional range in which clear, stable nanoemulsions were formed. This diagram served as a guide for selecting suitable ratios of formulation components and for preparing preliminary and factorial batches.





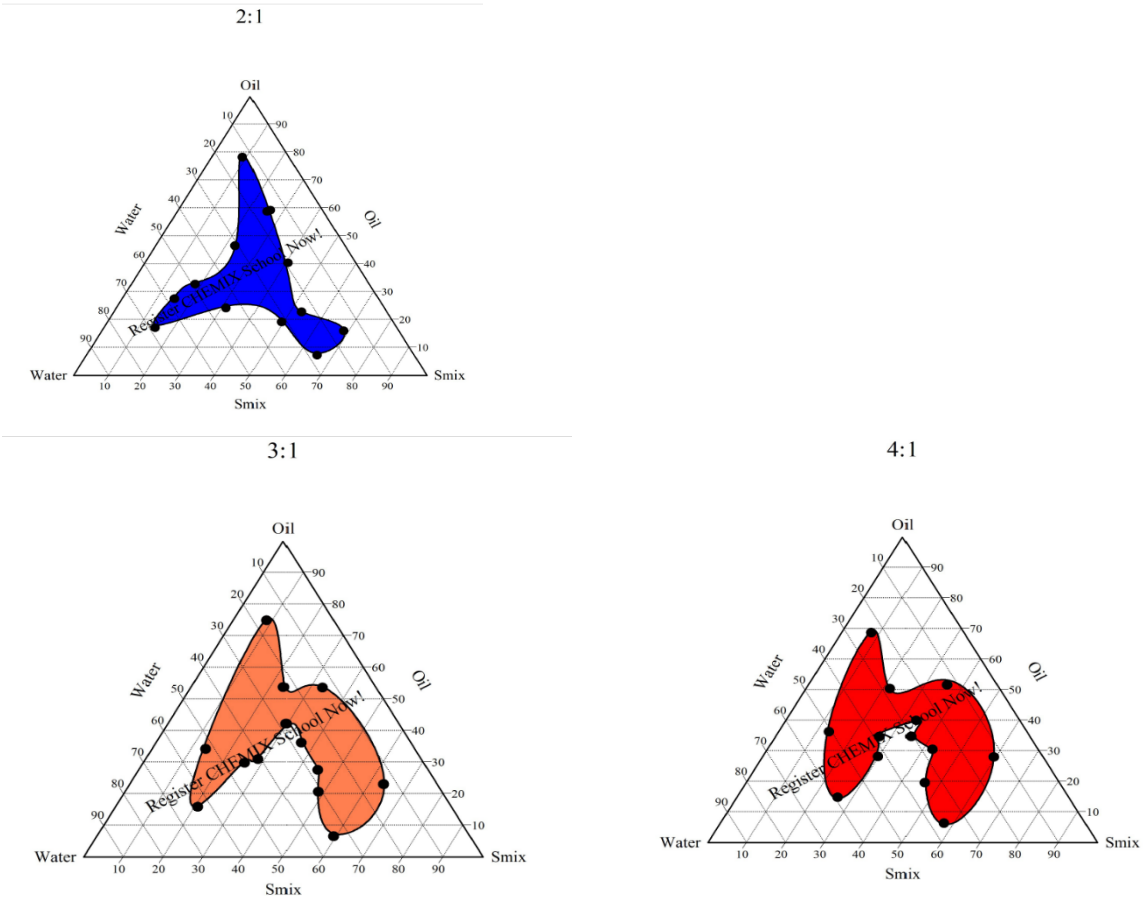


Figure 5. Construction of a pseudo-ternary phase diagram

Preliminary Trial Batches Based on Pseudo ternary Phase Diagram

Table 1 summarizes the composition of the preliminary nanoemulsion batches (LOV1–LOV3) with varying oil, Smix, and water concentrations. This provides the basis for understanding how component ratios influence nanoemulsion formation and stability.

Table: 1 Preliminary trial batches based on pseudo ternary diagram

Batch	Composition of Nanoemulsion (%)			Formula of Nanoemulsion		
	Oil (%)	Smix (%)	Water (%)	Oil (w/w)	Smix (w/w)	Water (w/w)
LOV1	5.59	55.54	34.53	1.274	7.242	11.48
LOV2	10.12	49.83	33.61	2.58	7.098	10.32
LOV3	17.83	43.37	32.86	3.922	9.03	7.04

Table:2 Effect of Nanoemulsion Composition on Transmittance, Viscosity, and Drug Release (8 hrs)

Batch	%Transmittance	Viscosity	%Drug Release (8 hrs)

LOV1	97.2	143	84.67
LOV2	97.5	148	85.67
LOV3	96.5	153	86.97

Table 2 presents the impact of the formulation composition on key performance parameters, including percent transmittance, viscosity, and percent drug release at 8 h. The data demonstrate that increasing the oil concentration slightly increases viscosity while influencing clarity and drug release behavior.

Formulation and Development of Lovastatin-loaded Nanoemulsion using Design of Experiment [DoE] Approach

Various batches of lovastatin nanoemulsions were prepared using the DoE approach according to a 32 factorial design, as follows:

Table: 3 Independent and Dependent Variables of32 Factorial Design

Independent Variables of Formulation			
Independent Variables	Low (-)	Medium (0)	High (+)
Oil concentration (X1)	2%	5%	8%
Smix concentration (X2)	40%	50%	60%
Dependent Variables			
Y1=% Transmittance			
Y2=Viscosity			
Y3=% Drug release			

Composition of 3^2 Factorial Nanoemulsion Batches

Table 4 lists nine factorial batches (LOVNE1–LOVNE9) with coded and decoded levels of oil and Smix concentrations. It shows how the formulation variables were systematically varied to study their effects on the response parameters.

Table: 4 Composition of 3^2 Factorial Nanoemulsion Batches

Nanoemulsion 3^2=9Batches				
Batch No	**Variable level in coded form**		**Variable level in decoded form**	
	Oil concentration (X1)	**Smix Concentration (X2)**	**Oil Concentration (X1)**	**Smix Concentration (X2)**

LOVNE1	-1	-1	2	40
LOVNE2	-1	0	2	50
LOVNE3	-1	+1	2	60
LOVNE4	0	-1	5	40
LOVNE5	0	0	5	50
LOVNE6	0	+1	5	60
LOVNE7	+1	-1	8	40
LOVNE8	+1	0	8	50
LOVNE9	+1	+1	8	60

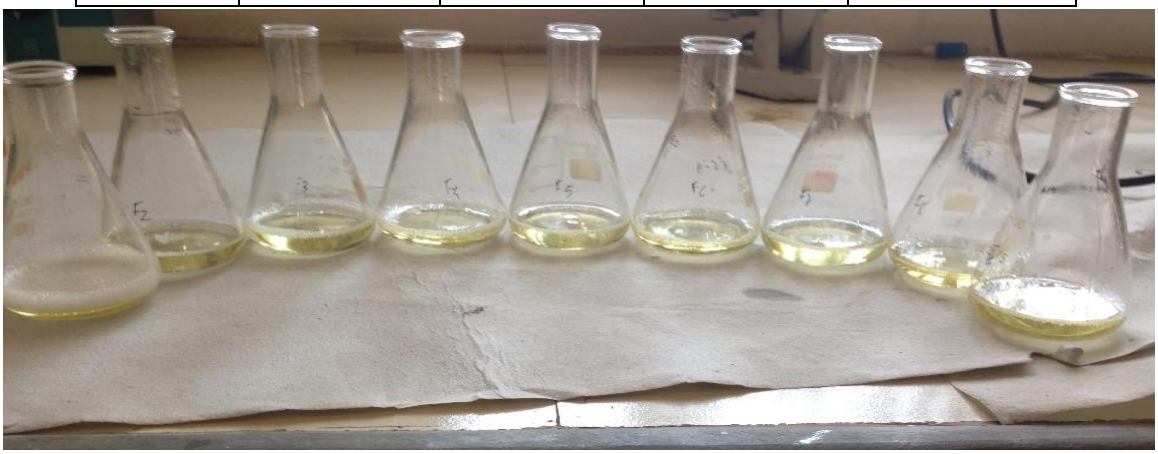


Figure 6. Batches LOVNE1 – LOVNE9

Characterization of Factorial Nanoemulsion Batches

Table 5 summarizes the experimental results for percent transmittance, viscosity, and percent drug release for all factorial batches. The data highlight the influence of the formulation variables and assist in identifying the optimized batch.

Table 5 Characterization of Factorial Nanoemulsion Batches

Batch No	% Transmittance (Y1)	Viscosity (Y2)	% Drug Release (Y3)
LOVNE1	98.8	149	84.67
LOVNE2	98.9	146	85.67
LOVNE3	99.4	144	89.67
LOVNE4	98.4	154	82.37
LOVNE5	98.6	152	86.67
LOVNE6	99.3	149	85.67
LOVNE7	92.6	166	82.37

LOVNE8	93.6	162	89.34
LOVNE9	94.4	159	79.67

Statistical Analysis

Response 1: Percent Transmittance

The effects of the formulation variables on percent transmittance (Response 1) were evaluated using a quadratic response surface model generated from a 3^2 factorial design. The developed polynomial equation describing the relationship between the independent variables and transmittance is given below:

Transmittance=+98.59-2.60* A+0.55* B+0.30* AB-2.63* A2+0.42* B2

where **A** and B represent the oil and Smix concentrations, respectively.

Interpretation of the Regression Equation

The positive intercept value (98.59) indicates high baseline transmittance, confirming the formation of clear nanoemulsions. The negative coefficient of oil concentration (A) (–2.60) suggests that increasing oil concentration significantly decreases percent transmittance, resulting in reduced clarity of the nanoemulsion. This may be attributed to increased droplet size and light scattering at higher oil levels.

In contrast, the positive coefficient of the Smix concentration (B; +0.55) indicates that a slight increase in the Smix concentration enhances transmittance by improving emulsification efficiency and reducing interfacial tension. The interaction term (AB) shows a small positive effect, suggesting a minimal synergistic interaction between oil and Smix on transmittance.

The significant negative quadratic term for oil concentration ($A^2 = -2.63$) demonstrates a pronounced curvature effect, indicating that the transmittance decreases sharply beyond the optimal oil concentration. The quadratic term for Smix (B^2) is small and statistically insignificant, suggesting a nearly linear influence of the Smix concentration within the studied range.

The ANOVA results for the quadratic model are summarized in Table 6. The model exhibited a high F-value (63.54) with a p-value of 0.0030, confirming that the model was statistically significant and suitable for explaining the variation in the percent transmittance.

Among the individual model terms,

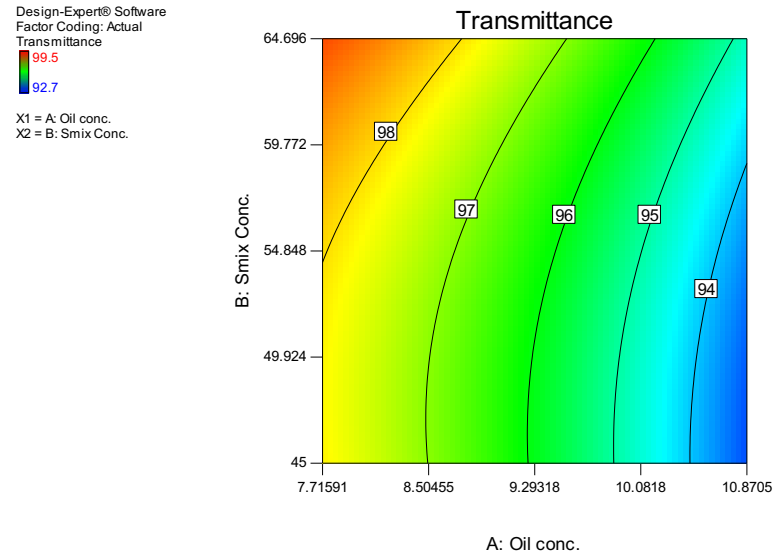
- Oil concentration (A) had a highly significant effect on transmittance ($F = 226.26$, $p = 0.0006$), indicating that it is the most influential variable affecting clarity.
- Smix concentration (B) also had a statistically significant effect ($F = 10.12$, $p = 0.0500$); however, its influence was less pronounced than that of the oil concentration.
- The interaction term (AB) was found to be statistically insignificant ($p = 0.2514$), suggesting that oil and Smix act independently with respect to transmittance.
- The quadratic term A^2 was statistically significant ($p = 0.0031$), confirming the presence of curvature in the response due to oil concentration.
- The quadratic term B^2 was insignificant ($p = 0.2582$), indicating no strong nonlinear effect of the Smix concentration on the transmittance within the experimental range.

The low residual sum of squares (0.54) indicates minimal unexplained variability, demonstrating a good fit between the experimental and predicted values.

Table 6. ANOVA for Response Surface Quadratic model

Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		**Mean**	**F**	**p-value**	
Source	**Squares**	**df**	**Square**	**Value**	**Prob > F**	
Model	56.95	5	11.39	63.54	0.0030	significant
A-Oil conc.	40.56	1	40.56	226.26	0.0006	
B-Smix Conc.	1.81	1	1.81	10.12	0.0500	
AB	0.36	1	0.36	2.01	0.2514	
A^2	13.87	1	13.87	77.37	0.0031	

B^2	0.35	1	0.35	1.94	0.2582	
Residual	0.54	3	0.18			
Cor Total	57.49	8				



Response Surface Plot

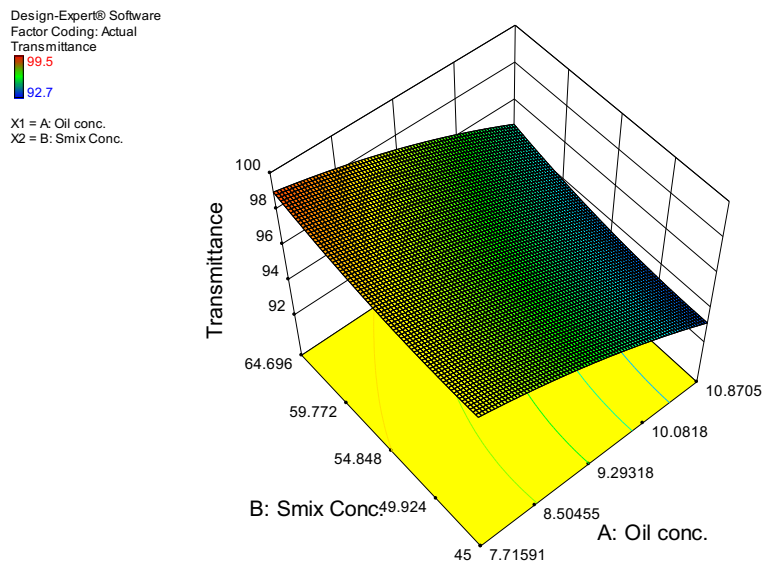


Figure 7: 3D Surface Plot

Statistical Analysis of Response 2: Viscosity

The influence of formulation variables on the viscosity (Response 2) of the lovastatin nanoemulsion was evaluated

using a quadratic response surface model derived from a 3^2 factorial design. The relationship between the independent variables and viscosity is expressed by the following polynomial equation:

$$\textbf{Viscosity} = 140.67 + 8.33A - 3.00B - 0.75AB + 2.00A^2 + 0.00B^2$$

where A and B denote the oil and Smix concentrations, respectively.

The ANOVA results, shown in Table 7, demonstrate that the quadratic model for viscosity is highly significant, with a model F-value of 266.35 and a p-value of 0.0004, confirming the suitability of the model for explaining viscosity variations.

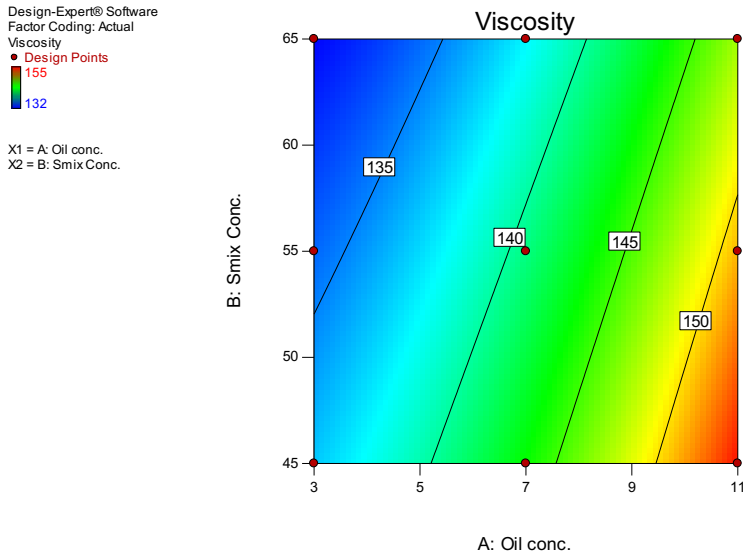
Among the individual factors,

- Oil concentration (A) had a highly significant effect on viscosity ($F = 1153.85$, $p < 0.0001$), indicating that it is the most influential factor governing the flow behavior of the nanoemulsion.
- The smix concentration (B) also had a significant effect ($F = 149.54$, $p = 0.0012$), indicating that surfactant concentration plays an important role in viscosity modulation.
- The interaction term (AB) was not statistically significant ($p = 0.0880$), suggesting that oil and Smix primarily influence viscosity independently, rather than synergistically.
- The quadratic term, A^2, was statistically significant ($p = 0.0181$), confirming the nonlinear behavior of viscosity at higher oil concentrations.
- The quadratic term B^2 was insignificant ($p = 1.0000$), indicating the absence of curvature effects for the Smix concentration.

The low residual sum of squares (1.08) reflects minimal unexplained variability, indicating excellent agreement between the experimental and predicted viscosity values.

Table: 7 ANOVA for Response Surface Quadratic model

Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		**Mean**	**F**	**p-value**	
Source	**Squares**	**df**	**Square**	**Value**	**Prob > F**	
Model	480.92	5	96.18	266.35	0.0004	significant
A-Oil conc.	416.67	1	416.67	1153.85	< 0.0001	
B-Smix Conc.	54.00	1	54.00	149.54	0.0012	
AB	2.25	1	2.25	6.23	0.0880	
A^2	8.00	1	8.00	22.15	0.0181	
B^2	0.000	1	0.000	0.000	1.0000	
Residual	1.08	3	0.36			
Cor Total	482.00	8				



Response Surface Plot

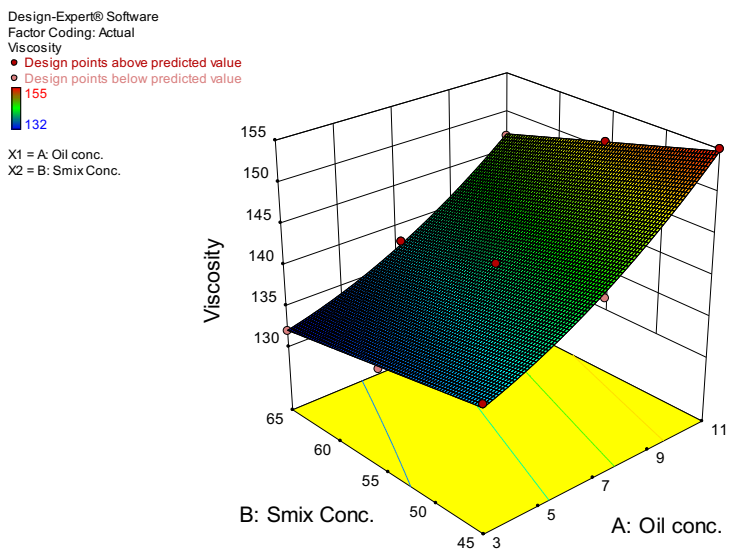


Figure 8: 3D Surface Plot

Statistical Analysis of Response 3: Percent Drug Release

The effects of formulation variables on the percent drug release (Response 3) from the lovastatin nanoemulsion were evaluated using a quadratic response surface model derived from a 3^2 factorial design. The mathematical relationship between the independent variables and drug release is expressed by the following polynomial equation:

$$\textbf{Drug Release} = 17.49 - 6.54A + 2.55B - 0.085AB - 0.38A^2 + 0.49B^2$$

where A and B represent the oil and Smix concentrations, respectively.

The ANOVA results demonstrate that the quadratic model for% drug release is statistically significant, with an F-value of 158.86 and a p-value of 0.0008, confirming the adequacy of the model to describe the experimental data.

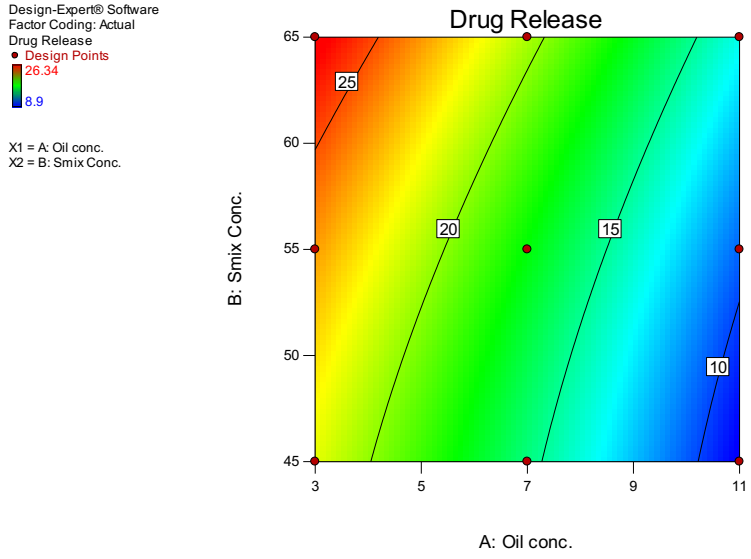
Among the model terms: Table 8

- Oil concentration (A) had a highly significant negative effect on drug release (F = 687.95, p = 0.0001), indicating that it was the most influential factor.
- Smix concentration (B) also had a significant positive effect (F = 104.18, p = 0.0020), indicating its important role in enhancing drug release.
- The interaction term (AB) was not statistically significant (p = 0.7988), suggesting that oil and Smix independently influenced drug release.
- The quadratic terms A^2 (p = 0.4437) and B^2 (p = 0.3349) were insignificant, indicating the absence of strong nonlinear effects at the studied levels.

The low residual sum of squares (1.12) reflects minimal experimental error and excellent agreement between the predicted and observed drug release values.

Table :8 ANOVA for Response Surface Quadratic model

Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		**Mean**	**F**	**p-value**	
Source	**Squares**	**df**	**Square**	**Value**	**Prob > F**	
Model	296.30	5	59.26	158.86	0.0008	significant
A-Oil conc.	*256.63*	*1*	*256.63*	*687.95*	*0.0001*	
B-Smix Conc.	*38.86*	*1*	*38.86*	*104.18*	*0.0020*	
AB	*0.029*	*1*	*0.029*	*0.077*	*0.7988*	
A^2	*0.29*	*1*	*0.29*	*0.77*	*0.4437*	
B^2	*0.49*	*1*	*0.49*	*1.31*	*0.3349*	
Residual	1.12	3	0.37			
Cor Total	297.42	8				



Response Surface Plot

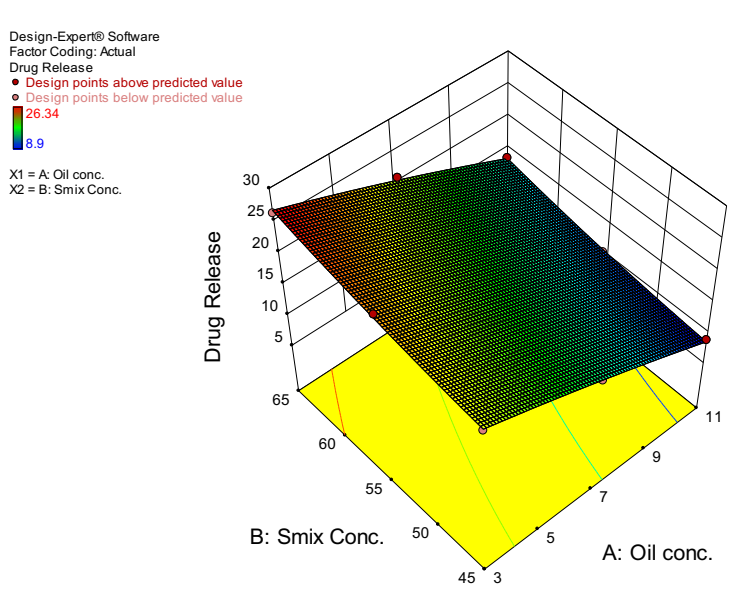


Figure 9: 3D Surface Plot

Statistical analysis revealed that oil concentration was the most influential formulation variable, significantly affecting percent transmittance, viscosity, and drug release. Increasing oil concentration reduced nanoemulsion clarity and drug release while increasing viscosity. In contrast, Smix concentration exerted a positive effect, improving transmittance and drug release while reducing viscosity by enhancing emulsification efficiency. Interaction effects between oil and Smix were statistically insignificant, indicating independent contributions of both variables. Overall, an optimized balance of lower oil concentration and adequate Smix levels is essential to achieve high clarity, suitable viscosity, and enhanced drug release, justifying the selection of the optimized nanoemulsion formulation for further development.

Check point analysis of validation batches

The predicted and actual responses refer to the comparison between the expected (predicted) and experimentally observed results for the validation batches of the lovastatin nanoemulsion formulation. The prediction response represents the values estimated by the statistical or mathematical model used during the formulation optimization process, based on the selected levels of independent variables, such as oil concentration (X1) and Smix concentration (X2). In contrast, the actual response reflects the measured experimental outcomes obtained after preparing and testing the validation batches under specified conditions.

For example, in batch 1 with an oil concentration of 4% and Smix concentration of 60%, the predicted values were 98.34% transmittance, 142.08 cP viscosity, and 84.67% drug release. The actual measured values for this batch were slightly different but close: 99.45% transmittance, 140.78 cP viscosity, and 86.46% drug release. Similarly, batch 2 with 4.5% oil and 50% Smix had predicted values of 97.67% transmittance, 146.58 cP viscosity, and 82.97% drug release, whereas the actual values were 96.78% transmittance, 144.63 cP viscosity, and 84.34% drug release.

This close agreement between the predicted and actual responses validated the reliability and accuracy of the optimization model in forecasting formulation performance, supporting the selection of Batch 1 as the optimized formulation for further development.

Selection of Optimized Formulation

Batch 1 was selected as the validated optimized formulation due to its superior performance characteristics, including a high percent transparency of 99.45%, indicating excellent clarity and homogeneity of the nanoemulsion. It exhibited a viscosity of 140.78 cP, which is suitable for topical application, balancing fluidity and stability. Additionally, the batch demonstrated 86.46% drug release, reflecting efficient and sustained drug availability from the formulation. These parameters collectively confirm that batch 1 meets the desired criteria for an effective lovastatin nanoemulsion, making it the preferred choice for further development and consideration for tablet formulation. The optimized nanoemulsion formulation and its characterization details provide a foundation for advancing the formulation toward practical pharmaceutical use.

In-Vitro Drug Release study

An in vitro drug release study was conducted to evaluate the release profile of lovastatin from the formulated

nanoemulsion over a specified period. Using a United States Pharmacopeia (USP) Type II dissolution apparatus, the nanoemulsion was subjected to a phosphate buffer medium (pH 7.4) maintained at physiological temperature (37 ± 0.5°C) with controlled stirring. Samples were withdrawn at predetermined intervals, typically hourly, for up to 8 h and analyzed spectrophotometrically to measure the amount of drug released from the nanoparticles. This study provides critical data on the rate and extent of lovastatin release from the nanoemulsion, demonstrating the formulation's capability to enhance drug dissolution compared to conventional forms. These results inform the optimization of formulation parameters to achieve sustained and efficient drug delivery.

Dose Calculation for Loading Lovastatin Nanoemulsion into Topical Gel

The marketed Lovastatingel formulation contains 1% w/w lovastatin, which means that

$$100 \text{ g formulation} = 1000 \text{ mg (1 g) Lovastatin}$$

To determine the required amount of Lovastatin for incorporation into 20 g of the nanoemulsion-based carbopol gel, the following proportional calculation was applied:

$$\frac{100 \text{ g formulation}}{1000 \text{ mg Lovastatin}} = 20 \text{ g formulation} \Rightarrow X \text{ mg Lovastatin}$$

$$X = \frac{1000 \times 20}{100} = 200 \text{ mg}$$

Thus, 200 mg of lovastatin was required to formulate 20 g of a nanoemulsion-based topical gel containing 1% w/w lovastatin.

Preliminary Trial batches

Table 9 presents the formulation design of the preliminary topical gel trial batches (LNEG1–LNEG3) prepared to select an appropriate gel base for incorporating the optimized lovastatin nanoemulsion. The concentration of carbopol 980 was varied (1–2% w/v) to study its effect on gel consistency, viscosity, and spreadability, whereas the amounts of propylene glycol, preservatives, triethanolamine, and water were kept constant. This approach enabled a systematic evaluation of the influence of polymer concentration on gel characteristics and facilitated the selection of a suitable base for the final nanoemulgel formulation.

Table 9 Formulation Design of Topical Gel Trial Batches

Ingredient	LNEG1	LNEG2	LNEG3
Carbopol 980 (%w/v)	1	1.5	2
Propylene glycol(mL)	5	5	5
Methyl paraben	0.1	0.1	0.1
Propyl paraben	0.05	0.05	0.05
Triethanolamine(mL)	0.25	0.25	0.25
Water(mL)	100	100	100

Table: 10 Evaluation of Carbopol gel

Ingredient	Colour	Odour	pH (Mean ± S.D.) (n = 3)	Viscosity Spindleno:61 (Mean ± S.D.) (n = 3)	Spreadability (gm.cm/sec) (Mean ± S.D.) (n = 3)
LNEG 1	**Colourless**	**Odourless**	**6.2±0.01**	**9015±43**	**14.45±0.34**

LNEG 2	Colourless	Odourless	6.0±0.03	9549±54	9.28±1.37
LNEG 3	Colourless	Odourless	6.3±0.01	11658±15	7.3±1.68

Table 10 summarizes the physical evaluation of the Carbopol gel trial batches (LNEG1–LNEG3). All formulations were colorless and odorless, indicating good aesthetic acceptability. The pH values (6.0–6.3) were within the acceptable range for topical application, suggesting skin compatibility. An increase in Carbopol concentration resulted in a progressive increase in viscosity and a corresponding decrease in spreadability. Among the batches, LNEG1 (1% Carbopol) exhibited optimum viscosity and the highest spreadability, making it the most suitable gel base for incorporating the optimized lovastatin nanoemulsion.

An in vitro release study of the optimized batch evaluated the drug release profile of lovastatin from the formulation over a specified period. This study measured the percentage of drug released at various time intervals, demonstrating gradual and sustained release. A stability study assessed the physical and chemical stabilities of the optimized formulation at room temperature for 30 days. Key parameters, such as spreadability, viscosity, and drug content, were monitored at the start, after 15, and 30 days. The results showed minimal changes in these parameters, indicating that the formulation maintained its consistency, flow properties, and drug potency over the storage period, thereby confirming its stability and suitability for further development.

DISCUSSION

In the present study, we successfully developed a lovastatin-loaded nanoemulsion and its corresponding nanoemulgel to address the poor aqueous solubility and limited dissolution of lovastatin. As a BCS class II drug, lovastatin requires solubility enhancement to improve its therapeutic performance [1–3]. The selection of oleic acid, Tween 80, and propylene glycol was based on their superior solubilization and emulsification efficiencies, consistent with reported nanoemulsion formulation strategies [4–6].

The pseudo-ternary phase diagram confirmed the formation of stable nanoemulsions, whereas a factorial design revealed that oil concentration negatively affected transmittance and drug release but increased viscosity. In contrast, Smix improved emulsification and drug release. These findings align with previous reports highlighting the critical role of formulation variables in nanoemulsion optimization [10–12].

The optimized nanoemulsion exhibited nanoscale droplet size, uniform distribution, and enhanced drug release (~86% in 8 h), attributed to increased surface area and improved solubilization [13–15]. Incorporation into a carbopol gel resulted in a nanoemulgel with suitable rheological properties and sustained drug release (~92% over 12 h), indicating controlled diffusion from the gel matrix. The release followed Higuchi kinetics, confirming the diffusion-controlled behavior typical of polymeric systems [16–19].

The formulation remained stable under storage conditions, demonstrating robustness and suitability for topical application [14,20]. Overall, this study highlights the effectiveness of combining nanoemulsion and gel systems with a DOE-based approach to enhance solubility and achieve controlled drug delivery.

Further studies, including ex vivo and in vivo evaluations, are warranted to confirm the clinical applicability of these results.

CONCLUSION

In the present study, we successfully developed and optimized a lovastatin-loaded nanoemulsion and its incorporation into a nanoemulgel system using a systematic design of experiments (DoE) approach. The optimized formulation exhibited improved solubility, high clarity, appropriate viscosity, and enhanced drug release, confirming the effectiveness of nanoemulsion-based delivery for poorly water-soluble drugs.

The nanoemulsion gel demonstrated suitable physicochemical properties and sustained drug release, indicating its potential for controlled topical delivery. The integration of nanoemulsion technology with a gel matrix provides a stable and patient-compliant formulation with improved performance compared to conventional systems.

In conclusion, this study establishes a rational formulation strategy for enhancing the solubility and achieving controlled drug delivery of lovastatin. Further investigations, including ex vivo permeation and in vivo studies, are required to validate its therapeutic applicability.

Limitations

This study is limited to in vitro evaluation; ex vivo or in vivo studies were not conducted to confirm drug permeation and therapeutic performance. Long-term stability studies under ICH conditions and comparisons with marketed formulations were also not conducted. Further investigations are required to validate the clinical applicability of the developed system.

Conflict of Interest

The authors declare no conflicts of interest related to the publication of this research work.

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